REMARKS

Claims 1-10 were pending prior to entering the amendments.

The Amendments

Claims 1-10 are cancelled.

New Claims 11-20 have been added.

New Claim 11 is supported by Claims 1, 2, and 9 as filed, and the specification at page 10, third full paragraph.

New Claims 12, 13, 14, 15, and 19 are supported by Claims 3, 4, 5, 6, and 10, respectively.

New Claims 16 and 17 are supported by page 4, line 8.

New Claim 18 is supported by page 4, lines 10-11.

New Claim 20 is supported by the specification at page 1, first paragraph.

No new matter is added in the amendments. The Examiner is requested to enter the amendments.

The Response

35 U.S.C. §101 Rejection

Claims 9-10 are rejected under 35 U.S.C. §101 allegedly because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process.

Claims 9-10 are cancelled. New Claim 11 has set forth the step involved in a process.

35 U.S.C. §112, Second Paragraph Rejection

Claims 9-10 are rejected under 35 U.S.C. §112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 9 and 10 are cancelled.

Claim 11 recites that the AAV vector carries at least one mutation in a heparin-binding motif of a capsid protein and causes a reduced or eliminated heparin binding function, wherein said mutation is an amino acid substitution at amino acid position arginine 484 and/or arginine 585. Claim 11 recites the location of the mutation in a heparin-binding motif of a capsid protein;

the mutation causes a reduced or eliminated heparin binding function. The mutation has been identified by its location and by its function.

Further, Claim 11 has recited the method step. Therefore, the §112, second paragraph rejection should be withdrawn.

35 U.S.C. §112, First Paragraph Rejection

Claims 9-10 are rejected under 35 U.S.C. §112, first paragraph, as allegedly failing to comply with the written description requirement.

Claims 9-10 are cancelled. New Claim 11 recites the genus of R484 and R585 as suggested by the Examiner. Therefore, the §112, first paragraph rejection should be withdrawn.

35 U.S.C. §103(a) Rejection

Claims 9-10 are rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Bartlett et al. (U.S. Patent No. 6,962,815, issued November 8, 2005) in view of Kaplitt et al. (U.S. Patent No. 6,162,796, issued December 19, 2000). The rejection is traversed.

The present invention

The new claims have been amended to limit to specific mutations at amino acid position arginine 484 and/or arginine 585; such specific mutations are not disclosed in any of the cited references. The basis for the identification of mutations is the concise characterization of amino-acids involved in binding heparan sulphate proteoglycan using a systematic analysis.

Bartlett (US 6,962,815 B2)

The findings reported by Bartlett do not give any information on amino-acids involved in binding heparan sulphate proteoglycan. Instead, Bartlett shows positions which are suitable for adding targeting peptides, which enable transduction independent of binding heparan sulphate proteoglycan (details see below).

(a) "The cellular range of tropism of the virus is determined by the binding of AAV capsid protein(s) to receptor and/or coreceptor proteins expressed on the surface of target cells.

Heparin-sulfate proteoglycans (HSPG) is the primary cellular attachment receptor for AAV2." (Bartlett, Column 2, lines 11-19).

This is a general remark about AAV transduction and its receptors and the state of the art when Bartlett filed his application. Bartlett focuses on analysis of different sites for integration of targeting motifs, but not on mutations of single amino acids or targeted modulation of binding to heparan sulphate proteoglycan.

(b) "AAV vectors of the invention that differ from wild type in that the natural tropism of AAV may be reduced or abolished by insertion or substitution of amino acids of interest in a capsid protein of the vector" (Bartlett, Column 4, lines 41-45)

This again refers to AAV vectors with insertion of targeting ligands into specific capsid regions and not to the modification of heparan sulphate proteoglycan binding by distinct mutations of the capsid.

(c) The examiner states that Bartlett further taught "amino acids 584 and 588 of VP1 as being important to heparin binding " and refers to Column 17, lines 1-7 and Column 41, line26 (Bartlett patent).

The examiner refers to an experiment (Column 17, lines 1-7) that allegedly reports transduction of cell lines with the "4C-RGD epitope following amino acids 584 and 588...in the presence of heparin sulfate." Bartlett then suggested that transduction takes place"via a HSPG-independent mechanism". This, however, does not imply that the 584- and 588-RGD vectors do not bind heparan sulphate proteoglycans any more, i.e. the endogenous tropism is ablated. The vectors still could enter cells via HSPG in addition to an HSPG-independent mechanism.

In conclusion, Bartlett's data do not provide any information as to the involvement of position 584 and 588 in heparin binding.

As a summary, since the new claims are limited to arginine 484 and/or arginine 585, which are not disclosed by Bartlett, the new claims are novel and non-obvious over Bartlett. In particular, Bartlett has not provided any information regarding change of heparin binding for improving transduction.

Kaplitt (US 6,162,796)

Kaplitt et al. reports the general use of AAV for gene transfer into the heart. The present invention, however, concerns a modified AAV that results in decreased liver transduction. As a potential result of decreased liver transduction, the inventors found a significantly increased cardiac transduction. This was not made foreseeable by Kaplitt.

(a) The examiner notes that "Kaplitt et al. do not teach the specific mutations of capsid proteins and its corresponding effect on heparin-sulfate binding proteins as taught by Bartlett et al.". This statement misinterprets Bartlett. Bartlett has not analyzed the effect of "specific mutations of capsid proteins and its corresponding effect on heparin-sulfate binding proteins". As outlined above, Bartlett taught positions, which are suitable for adding targeting peptides which enable transduction independent of binding heparan sulphate proteoglycan (Column 17, lines 1-7 Bartlett patent).

(b) The examiner concludes that "it would have been obvious to one skilled in the art to use an AAV vector having at least one mutation in the capsid proteins in amino acid positions 470 to 592, which affects heparin binding in a method of gene therapy to heart muscle tissue" (Office Action at page 11, line 15). This conclusion is not justified since the basis for the identification of the claimed method/positions is the concise characterization of amino-acids involved in binding heparan sulphate proteoglycan, which have not been reported before. The most promising mutations have been combined and resulted in an unexpectedly reduced transduction of the liver and significantly increased transduction of the heart, while other tissues also revealed a tendency to increased transduction levels.

The inventors performed the first systematic analysis of heparin binding of distinct capsid mutations. A mutational analysis of the AAV capsid regarding HSPG-binding is not suggested by the Bartlett patent and Kaplitt patent.

Therefore, new Claims 11-20 are not obvious over Bartlett in view of Kaplitt.

CONCLUSION

Applicants believe that the application is in good and proper condition for allowance. Early notification of allowance is earnestly solicited.

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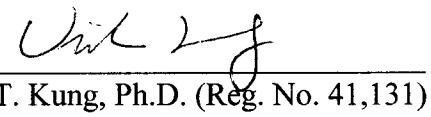
Respectfully submitted,



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